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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,070	03/03/2006	Sutisak Kitareewan	DC0266US.NP	5026

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
11/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/564,070	KITAREEWAN ET AL.	
	Examiner	Art Unit	
	PAUL C. MARTIN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *2-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group II (Claim 1) in the reply filed on 08/19/09 is acknowledged. The traversal is on the ground(s) that the present invention relates to compositions and methods for destabilizing lysosomes to increase the degradation of oncogenic or aberrant proteins for the prevention and treatment of disease while the cited '932 patent contemplates decreasing the processing of aberrant proteins by application of chloroquine. This is not found persuasive because the basis for restriction was whether the special technical feature, the chloroquine agent or derivatives, analogs or enantiomers thereof was a contribution over the Prior Art. As the '932 Patent teaches the use of chloroquine, the agent itself is not a contribution over the Prior Art and restriction is proper. Claims 2-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 08/19/09.

Claim 1 was examined on its merits.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of identifying an agent which destabilizes lysosomes, does not reasonably provide enablement for a method to identify any agent which destabilizes lysosomes and increases any oncogenic or aberrant protein degradation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands,* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation.

The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

1) The Quantity of Experimentation Necessary: The instant disclosure is directed to a screening method to identify an agent which destabilizes lysosomes thereby increasing oncogenic or aberrant protein degradation. The disclosure provides teachings directed to the exposure of cell lysates or isolated lysosomes being contacted with arsenic and observation of degradation of (oncogenic) PML/RARα or (aberrant) CFTR proteins in the reaction mixtures (Specification, Pg. 5, Lines 1-31). The disclosure does not teach examples of any other agents having this property, the other lysosomal targeting drugs tested (imipramine, chloroquine and N-octyl-D-erythro-spingosine) were only tested for their ability to inhibit the growth of retinoic acid sensitive and retinoic acid resistance cells Specification, Pg, 6, Lines 1-26).

The results indicate that chloroquine and retinoic acid suppressed growth in retinoic acid resistant and sensitive cells (Figs. 1A and 1B) and that chloroquine increased apoptosis in retinoic acid sensitive cells (Pg. 7, Table 1). The disclosure does not indicate a concomitant increase in protein degradation of either oncogenic or aberrant proteins in response to chloroquine, nor if chloroquine actually destabilizes lysosomes at all. Therefore, one of ordinary skill in the art would have to test innumerable compounds both for lysosomal destabilizing properties as well as protein degradation as not all destabilizing agents increase protein degradation of aberrant or oncogenic proteins.

2) The Amount of, or Direction of Guidance Presented: As discussed above, the instant disclosure only provides one example wherein an agent was shown to both destabilize lysosomes and increase degradation of (oncogenic) PML/RARα or (aberrant) CFTR proteins in the reaction mixtures. The disclosure broadly indicates that the same process can be used to identify other agents however no other agents are disclosed which have the properties of increasing protein degradation and destabilizing lysosomes. Other preferred embodiments, chloroquine and retinoic acid, were shown to have both apoptosis inducing and growth suppressing properties and growth suppressing properties respectively on certain cells types but nowhere is either specifically shown to physically destabilize lysosomes and increase the degradation of either oncogenic or aberrant proteins.

3) The Presence or Absence of Working Examples: As discussed above, the instant disclosure only provides one example wherein an agent was shown to both destabilize lysosomes and increase degradation of (oncogenic) PML/RARα or (aberrant) CFTR proteins in the reaction mixtures. No other agent was identified which has these properties.

4) The Nature of the Invention: The invention requires that an agent be identified which has both the ability to destabilize lysosomes (lacking a definition the Examiner has interpreted the term to mean any agent which disrupts the lysosome activity) and concurrently increase the degradation of either or both of oncogenic or aberrant proteins.

5) The State of the Prior Art: Bahr (US 2002/0094958 A1, cited in IDS) teaches that chloroquine is a known agent of lysosomal activity disruption and targets pH-dependent enzymes by disrupting the proton gradient of lysosomes (Pg. 5, Paragraph [0054] and creates aberrant protein processing/aggregation within neurons (Pg. 5, Paragraph [0050]). Nowhere is indicated that chloroquine can either destabilize the lysosome such that the lysosomal membrane is disrupted or that degradation of either or both of oncogenic or aberrant proteins occurs. Ikezoe *et al.* (2009) teaches that chloroquine raises the pH in the lysosomal lumen and causes disruption of lysosomal function (Pg. 575, Column 1, Lines 33-35) and that chloroquine treated rats show increased levels of the aberrant protein Amyloid-β (Pg. 580, Fig. 5).

The state of the art indicates that chloroquine does not possess the property of destabilizing lysosomal membranes and in fact, leads to an increased aggregation of aberrant proteins.

6) The Relative Skill of those in the Art: The skill level of those in the relevant art (Biological Sciences) is deemed to be high.

7) The Breadth of the Claims: The Claims are directed to a screening method to identify an agent which destabilizes lysosomes thereby increasing oncogenic or aberrant protein degradation. The Disclosure however, only provides a single example wherein a compound (arsenic) both destabilizes lysosomes and leads to increased specific degradation solely of (oncogenic) PML/RARα or (aberrant) CFTR proteins in the reaction mixtures. No other oncogenic or aberrant proteins are shown to be increasingly degraded by exposure to arsenic, and of the two other preferred embodiments; chloroquine was shown to suppress growth in retinoic acid resistant cells and increase apoptosis in retinoic acid sensitive cells but not to have the specific property of destabilizes lysosomes and increasing specific degradation of oncogenic or aberrant proteins. In fact, chloroquine is known in the art to increase aggregation of aberrant proteins and not to destabilize lysosomal membranes.

The disclosure asserts that another preferred embodiment; retinoic acids, are useful in destabilizing lysosomes however no evidentiary support for this allegation is provided in the disclosure nor is discussed or taught the property of retinoic acids in increasing degradation of either or both of oncogenic or aberrant proteins.

Therefore, while being enabling for a method of identifying an agent which destabilizes lysosomes, does not reasonably provide enablement for a method to identify any agent which both destabilizes lysosomes and increases any oncogenic or aberrant protein degradation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 refers to the "destabilization" of lysosomes. As "destabilization" is defined by Webster's Dictionary as "to upset the stability or equilibrium of". It is unclear whether "destabilization" refers to physical disruption of the lysosomal membrane or any disruption of the lysosome.

Lacking a specific definition in the Disclosure, the Examiner has interpreted "destabilization" as any disruption of the lysosome activity or physical state.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Schütt *et al.* (2002).

Schütt *et al.* teaches that isolated, intact lysosomes can be destabilized (lysosomal membranes disrupted) by exposure to the lipofuscin retinoid component A2-E (N-retinylidene-N-retinylethanolamine) at concentrations above 2μM (Pg. 862, Abstract, Column 1, Lines 13-48).

The A2-E compound meets the limitations of the claimed invention, that is, an agent being able to destabilize the lysosome. The limitation of increasing oncogenic or aberrant protein degradation is deemed to be an inherent feature of the compound as the claim only requires contacting a lysosome with an agent and detecting whether said agent destabilizes the lysosome.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Öllinger *et al.* (1995).

Öllinger *et al.* teaches a method wherein cultured, rat hepatocytes containing lysosomes are contacted with napthazarin (5,8-dihydroxy-1,4-napthoquinone)and detecting whether the napthazarin destabilizes the lysosomes by monitoring acridine orange fluorescence (Pg. 570 Column 1, Lines 23-32 and Column 2, Lines 1-10 and Pg. 572. Fig. 5).

The napthazarin compound meets the limitations of the claimed invention, that is, an agent being able to destabilize the lysosome.

The limitation of increasing oncogenic or aberrant protein degradation is deemed to be an inherent feature of the compound as the claim only requires contacting a lysosome with an agent and detecting whether said agent destabilizes the lysosome.

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Weeks *et al.* (1996).

Weeks *et al.* teaches a method wherein test earthworms are exposed to copper containing soil and coelomocytes containing lysosomes are extracted and detection of whether the copper destabilizes the lysosomes is performed by monitoring neutral red uptake and loss by lysosomes (Pg. 1803, Fig. 1 and Pg. 1804, Fig. 2).

The copper compound meets the limitations of the claimed invention, that is, an agent being able to destabilize the lysosome. The limitation of increasing oncogenic or aberrant protein degradation is deemed to be an inherent feature of the compound as the claim only requires contacting a lysosome with an agent and detecting whether said agent destabilizes the lysosome.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjanuth Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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11/10/09

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